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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/588,314	06/06/2000	Brian S. Hooker	059440/0128	9635

7590 05/06/2003

David Latwesen
Wells St. John
West 601 First Ave.
Spokane, WA 99201-3828

EXAMINER	
SCHMIDT, MARY M	

ART UNIT	PAPER NUMBER
1635	16

DATE MAILED: 05/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/588,314	Applicant(s) HOOKER ET AL.	
	Examiner Mary M. Schmidt	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If the period for reply specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,12-15 and 18-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,12-15 and 18-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Application/Control Number: 09/588,314

Art Unit: 1635

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-10, 12-15 and 18-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons of record set forth in the Office action mailed 09/09/02.

Applicant's arguments filed 2/10/03 have been fully considered but they are not persuasive. Since applicants response is directed to both 35 U.S.C. 112, first paragraph rejections, the response to arguments is found below.

Claim 12 is included in the instant rejection since it remains drawn to any active human coagulation factor VIII and is not limited to the specific full-length human coagulation factor VIII shown in the instant specification. Thus the claim reads broadly on modifications of the human coagulation factor VIII shown in the instant specification and is rejected for the same reasons of record set forth in the Office action mailed 09/09/02.

3. Claims 1-10, 12-15 and 18-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of expression of a full-length human or porcine/human chimera coagulation factor VIII having a "bioactive" function in plants, does not reasonably provide enablement for methods of expression of any coding sequence having any fragment and/or modification of human or chimera coagulation factor VIII as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for the same reasons of record set forth in the Office action mailed 09/09/02.

Applicant's arguments filed 2/10/03 have been fully considered but they are not persuasive.

Claim 12 is included in the instant rejection since it remains drawn to any active human coagulation factor VIII and is not limited to the specific full-length human coagulation factor VIII shown in the instant specification. Thus the claim reads broadly on modifications of the human coagulation factor VIII shown in the instant specification and is rejected for the same reasons of record set forth in the Office action mailed 09/09/02.

Response to Arguments

The claims remain drawn to a broad scope of methods of production of any size human coagulation factor VIII expressed in the plant cells as "active".

Applicant states on page 4 of the response that "[i]n the instant invention, one of skill in the art would have known at the time the application was filed which fragments and/or modifications would be suitable for use in the present invention. Indeed, scientific literature was available at the time of filing that describes the production of heterologous proteins in animal cell hosts, thereby teaching details of cloning and expression of both factor VIIIa (inactivation resistant coagulation factor VIII) and B-domain deleted factor VIII (now marketed as Refacto®). See, Exhibit A. Accordingly, the quantity of experimentation required to identify which nucleotide sequences encodes a functional human factor VIII protein, or which functional fragments would be suitable for use in the present invention, was not undue, but well within the level of the skilled artisan at the time the invention was made."

This argument is not persuasive since the instant specification as filed does not discuss at all making the B-domain deleted factor VIII or any other shorted variant of the factor VIII by the disclosed methods in plants. Thus, the specification as filed has not adequately described the breath of the claimed invention nor taught one skilled in the art how to make and use the breath of the claimed invention for proteins other than the full-length factor VIII.

Applicant further states that "Eaton describe a factor VIII deletion mutant wherein residues 797 through 1562 were omitted by standard molecular biology techniques.... and Toole teach factor VIII molecules missing 581 or 880 amino acids in the B domain.... Similarly, large B-domain deletions, such as amino acid residues 760 to 1639, also yielded a protein with similar specific activity compared to the wild-type molecule.... Furthermore, Pipe describe cloning and

expression of factor VIIIa.... In particular, Pipe teaches use of missense mutations at thrombin (Arg-740) and activated protein C inactivation cleavage sites to provide greater resistance to proteolysis. This reference also describes the detection of residues 794-1689 in factor VIII, so that the A2 domain is covalently attached to the light chain."

However, none of these specific protein designs were taught in the specification as filed, nor did the specification provide any indication that these proteins were considered functional variants of the full-length factor VIII protein for use in the claimed methods. Without this teaching in the specification as filed, one skilled in the art would not have recognized that application had adequately described these variants for use in the claimed methods.

Applicants further state that the cited Cramer et al. and Lollar et al. references "affirm that biologically active fragments and deletions of factor VIII cannot be expressed in plants...."

In response, the specification as filed only provides guidance for expression of the full-length factor VIII in plants. The argument that showing expression of full-length in plants provides a teaching of expression of any fragment or deletion of that protein in plants is not considered valid since the main reason the specification is not enabled for that fragments and deletions is not the mechanics of expression a smaller shaped protein, but rather is based on the fact that it is not disclosed in the specification what deletions and modifications may be made to retain the function of a protein that functions as a factor VIII protein. Without guidance for the specific changes that would retain factor VIII function, one skilled in the art would not be able to make and use the breath of the claimed proteins having factor VIII "activity" or function.

Applicant further states that "[t]he fundamental factual inquiry regarding the adequacy of disclosure is whether the application conveys with reasonable clarity to those skilled in the at that, as of the filing date sought, applicant was in possession of the claimed invention."

The arguments made previously and above revolve around the fact that there is no clear description in the specification of factor VIII variants other than the full-length human factor VIII, and as such one of skill in the art would not have recognized that applicant either contemplated or had possession of a representative number of species of other factor VIII active fragments at the time the invention was made.

4. The closest prior art to the claimed invention was cited in the previous Official Action mailed 10/02/01 as Cramer et al. in view of Hoeben et al., Healey et al., Lollar et al., Stein et al. and Lubin et al. which was relied upon to teach the expression of non-plant, such as human, proteins in tobacco plants (Cramer et al.) and the expression of human coagulation factor VIII and its use in mammals (Hoeben et al., Healey et al., Lollar et al., Stein et al. and Lubin et al.). The rejection was withdrawn in view of applicants declaration showing unexpected results for expression of full-length human coagulation factor VIII in plants because of its substantial size.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Katrina Turner*, whose telephone number is (703) 305-3413.

M. M. Schmidt
May 5, 2003

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600